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Controversies and future perspectives of antiplatelet therapy in secondary stroke prevention

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Abstract

Antiplatelet agents are a cornerstone in the treatment of acute arterial thrombotic events and in the prevention of thrombus formation. However, existing antiplatelet agents (mainly aspirin, the combination of aspirin and dipyridamole and clopidogrel) reduce the risk of vascular events only by about one quarter compared with placebo. As a consequence, more efficacious antiplatelet therapies with a reduced bleeding risk are needed. We give an overview of several new antiplatelet agents that are currently investigated in secondary stroke prevention: adenosine 5′-diphosphonate receptor antagonists, cilostazol, sarpogrelate, terutroban and SCH 530348. There are unique features in secondary stroke prevention that have to be taken into account: ischaemic stroke is a heterogeneous disease caused by multiple aetiologies and the blood–brain barrier is disturbed after stroke which may result in a higher intracerebral bleeding risk. Several small randomized trials indicated that the combination of aspirin and clopidogrel might be superior to antiplatelet monotherapy in the acute and early post-ischaemic phase. There is an ongoing debate about antiplatelet resistance. Decreasing response to aspirin is correlated independently with an increased risk of cardiovascular events. However, there is still no evidence from randomized trials linking aspirin resistance and recurrent ischaemic events. Similarly, randomized trials have not demonstrated a clinical significantly decreased antiplatelet effect by the concomitant use of clopidogrel and proton pump inhibitors. Nevertheless, a routine use of this drug combination is not recommended.

Keywords: thrombosis • antiplatelet • ischaemic stroke • prevention • aspirin resistance • clopidogrel • cilostazol • sarpogrelate • terutroban • SCH 530348

Introduction

Antiplatelet agents are the main drugs used nowadays to treat both acute arterial thrombotic events and to reduce the incidence of arterial thrombus formation in patients with cardiovascular disease. However, current antiplatelet agents reduce the risk of serious vascular events (non-fatal myocardial infarction, non-fatal stroke or vascular death) only by about 25% (relative percentage) [1]. In patients with a previous stroke or transient ischaemic attack (TIA), 36 vascular events are prevented among 1000 patients treated for 2 years and their use is associated with a substantial risk of bleeding. As a consequence, a new generation of safer and more effective antithrombotic drugs agents is needed in secondary stroke prevention.

In order to address antiplatelet drug therapy in stroke prevention and mechanisms of action of newer antiplatelets agents, a thorough knowledge of the complex process of thrombus formation and unique features in the pathophysiology of ischaemic stroke is needed. We will describe briefly the role of platelets in arterial thrombus formation and point out some important differences

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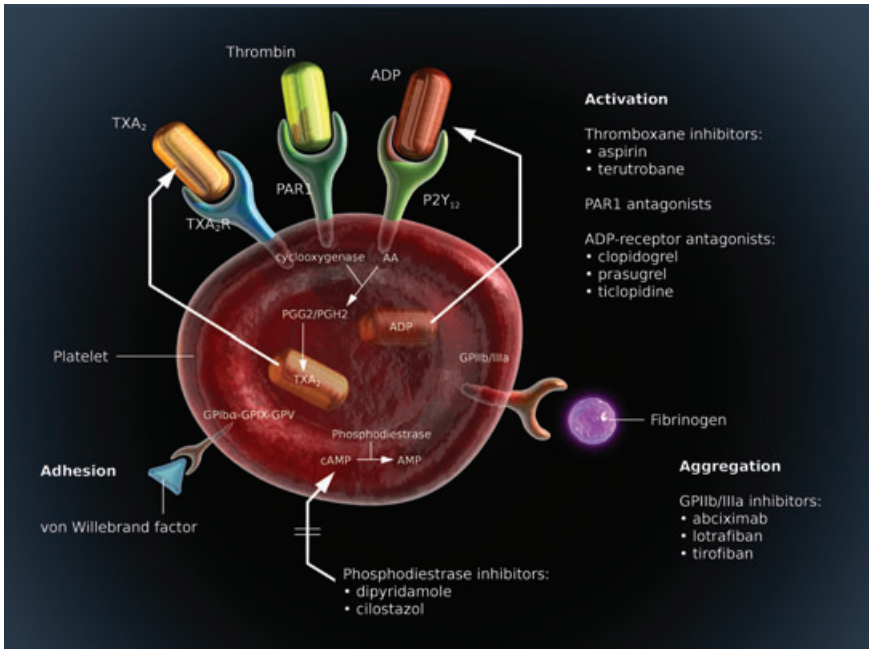

Fig. 1 Antiplatelet agents and their different mechanisms of action on platelet adhesion, activation and aggregation. vWF binds to the platelet glycoprotein (GP) Ib/V/XI-receptor and is responsible for platelet adhesion to the blood vessel wall. Platelet activation is mediated by a variety of cell-surface receptors (TXA_2 receptor; PAR1; ADP $P2Y_{12}$ receptor). Aspirin irreversibly inhibits the enzyme COX resulting in decreased production of prostaglandins (PGG2 and PGH2) and TXA_2 from arachidonic acid (AA). Platelet phosphodiesterase inhibitors lead to an increase in cyclic adenosine monophosphate and oppose actions of TXA_2, ADP, AA and other activating factors. Aggregation between platelets is mediated by binding of fibrinogen to the platelet GP IIb/IIIa-receptor. Reprinted from [6]. Copyright (2009), with permission from Taylor & Francis Ltd.

between ischaemic heart attack and stroke in the first part of our review. In the second part, we will focus on current controversies in antiplatelet therapy such as aspirin resistance, dual antiplatelet therapy with aspirin and clopidogrel in patients presenting with acute ischaemic stroke of arterial origin and the interaction between clopidogrel and proton pump inhibitors (PPIs). Finally, we give an update on new antiplatelet agents that are or have been recently investigated in secondary stroke prevention.

Thrombus formation and differences between ischaemic heart and brain disease

Platelets are pivotal in the pathogenesis of atherothrombosis and the complex cascade of blood coagulation. Platelets are also involved in the initiation and progression of atherosclerosis [2]. The arterial blood vessels are part of a high-flow and high-pressure system in which shear forces are present. Vascular injury exposes thrombogenic substances from the damaged vessel wall, which leads to platelet adhesion through the interaction of specific platelet cell-surface receptors (glycoprotein VI and Ib/V/XI) with collagen and von Willebrand factor (vWF) [3, 4]. Platelet adhesion stimulates platelet activation by various intracellular signalling pathways, which result in inside/out activation of the platelet glycoprotein IIb/IIIa receptors on the platelet surface and the release of mediators from the platelet, such as adenosine 5′-diphosphonate (ADP), thromboxane A_2 (TXA_2) and thrombin (factor II). Another major pathway of platelet activation involves the activation of the platelet protease-activator receptor (PAR) 1, which is also known as the thrombin receptor, by thrombin. Interactions among these various factors ensure redundancy in the pathways responsible for platelet activation. Simultaneously, the coagulation cascade results in local generation of fibrin, the main protein component of the thrombus. The recruitment and activation of adjacent platelets results in platelet aggregation and thrombus growth, a process mainly mediated by cross-linking of fibrinogen by the glycoprotein IIb/IIIa integrins. Thus, platelet and coagulation activation have been considered as ‘inseparable, reciprocally self-amplifying processes’ [5].

The primary target of available antiplatelet drugs is inhibition of platelet activation and aggregation (Fig. 1). At present, there are no drugs in routine clinical use that block the early step in thrombus formation, namely the binding of platelets to collagen and vWF. However, several new drugs which target the interaction of platelets with the vWF [6] are being developed. One of these, the nuclease resistant aptamer ARC1779 has been investigated in a randomized, double-blind and placebo-controlled dose-finding study trial in 47 healthy volunteers [7]. ARC1779 produced dose- and concentration-dependent inhibition of vWF activity and was well tolerated with no observed bleeding complications.

Ischaemic stroke is not a homogenous disease but is caused by various aetiologies: large artery atherosclerosis of the brain supplying extra- and intracranial blood vessels, cardiac embolism (mainly from atrial fibrillation) and cerebral microangiopathy of the small penetrating arteries. After all the cause of an ischaemic stroke remains unclear in up to 30% of ischaemic stroke patients or there are concurrent possible stroke mechanisms [8]. In contrast, acute myocardial infarction is almost exclusively caused by

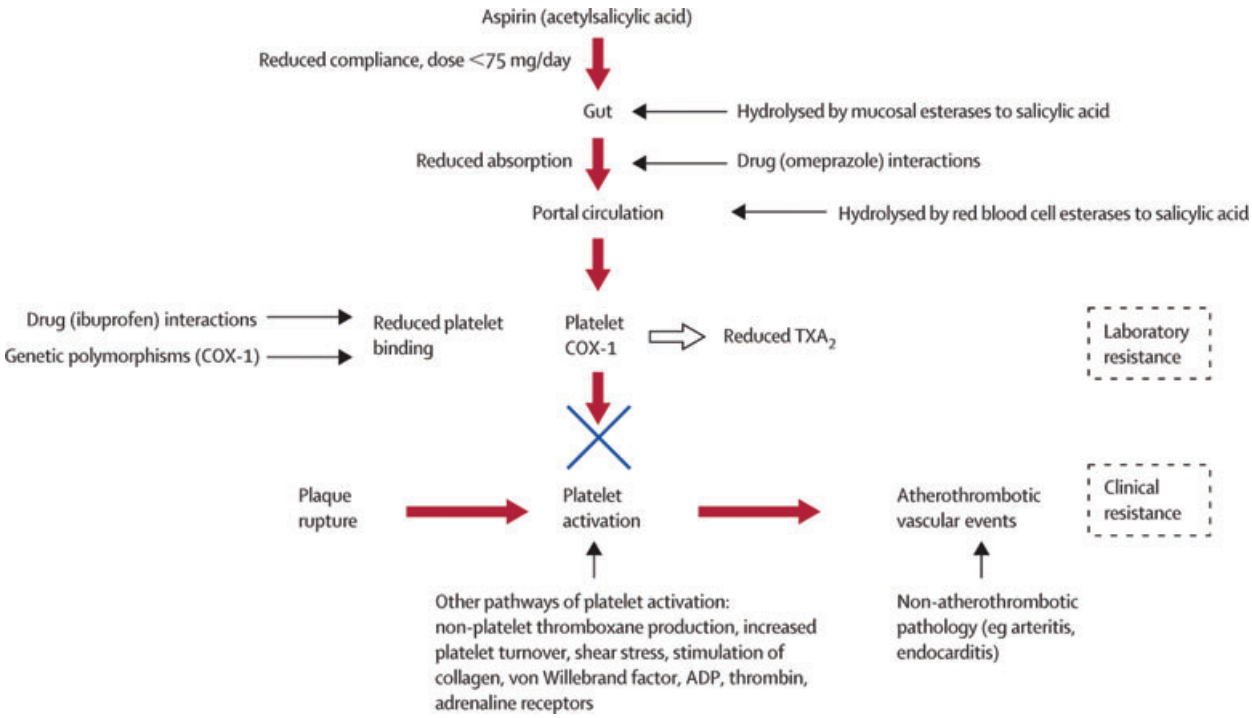

Fig. 2 Possible mechanisms of laboratory or clinical aspirin resistance. Reprinted from [15]. Copyright (2006), with permission from Elsevier.

large artery atherosclerosis due to atherosclerotic plaque rupture. Furthermore, endothelial cells of brain vessels are unique in that they express apical junctional complexes as part of the blood–brain barrier (BBB) which controls cerebral homeostasis [9, 10]. The BBB is altered after cerebral ischemia and reperfusion by oxidants, proteolytic enzymes, inflammation and therapeutic agents administered in acute stroke treatment such as recombinant tissue plasminogen activator [11–13]. These changes result in an increased BBB permeability which contributes to further brain damage, brain oedema formation and an increased risk of cerebral haemorrhage both in the acute and the chronic post-stroke phase. The increased bleeding risk has to be taken into account in the aged human brain when evaluating antiplatelet agents in secondary stroke prevention.

Aspirin resistance

As with other vascular prevention strategies (*i.e.* lowering of blood pressure or cholesterol), antiplatelet agents can reduce, but not abolish the risk for a recurrent cerebrovascular event. A meta-analysis of eleven randomized and placebo-controlled trials investigating aspirin monotherapy in secondary stroke prevention found a relative risk reduction of 13% (95% CI, 6–19%) for the combined end-point of stroke, myocardial infarction and vascular death [14]. However, there is a long-lasting debate about the phenomenon of 'aspirin resistance', whereas nobody is talking about 'statin resistance' in patients who face a recurrent thromboembolic event under treatment with a lipid lowering statin.

Aspirin resistance may be divided into laboratory resistance and clinical resistance. Laboratory resistance is defined as the failure of aspirin to inhibit platelet TXA_2 production or inhibit tests of platelet function that are dependent on thromboxane production by platelets [15]. Briefly, aspirin irreversibly inhibits the cyclooxygenase (COX)-1 enzyme in platelets by acetylation of a serine residue. The COX-1 enzyme catalyses the conversion of arachidonic acid to prostaglandin G_2/H_2, which is then catalysed by the thromboxane synthase to form TXA_2. TXA_2 acts as a platelet activator in different ways and is also a vasoconstrictor. The inhibition of COX-1 is rapid, saturable at low doses and permanent for the life of platelets because platelets are not able to synthesize new proteins [16]. Aspirin treatment failure or clinical resistance is defined as the failure to prevent recurrent thromboembolic ischaemic events. There are numerous possible causes of aspirin resistance including patients noncompliance, drug interactions (*i.e.* with NSAID), genetic polymorphisms of COX-1 and other genes involved in thromboxane production, increase biosynthesis of thromboxane by alternative sources (*i.e.* by COX-2 in macrophages or vascular endothelial cells) or increased platelet turnover (Fig. 2).

Results from a prospective sub-study of the heart outcomes prevention evalution (HOPE) trial involving 976 high-risk vascular

patients showed that patients in the highest quartile of urinary 11-dehydrothromboxane B_2 concentration (a marker of *in vivo* thromboxane generation) had an adjusted increased odds of a serious vascular event (stroke, myocardial infarction, vascular death) of 1.8 (95% CI, 1.2–2.7) over a median follow-up period of 4.5 years [17]. Decreasing response to aspirin is correlated independently with an increased risk of cardiovascular events in patients at risk [18]. However, there is still no evidence from randomized trials linking aspirin resistance and recurrent vascular ischaemic events in stroke patients. Furthermore, we do not know which antithrombotic therapy to use in patients who experienced a recurrent non-cardioembolic ischaemic stroke under treatment with aspirin: go on with the same aspirin dose, increase the aspirin dose, switch to another antiplatelet agent or use a combination antiplatelet therapy?

Another issue that has to be critically addressed is the lack of a gold standard in measuring antiplatelet functioning such as monitoring international normalized ratio in patients treated with vitamin K-antagonists. There are several methods available for monitoring platelet function and concerns have been raised about reproducibility and prognostic value of these methods [19, 20]. The Popular study evaluated prospectively the capability of five different platelet function tests to predict clinical outcome (primary end-point was a composite of all-cause death, myocardial infarction, stent thrombosis and ischaemic stroke) in 1069 consecutive patients undergoing elective coronary stenting followed by dual antiplatelet therapy with aspirin and clopidogrel (maintenance doses for aspirin were 80–100 mg/day and 75 mg/day for clopidogrel) [21]. The authors showed that only 3 of the 5 platelet function tests were significantly associated with the primary end-point at 1 year follow-up and that the predictive accuracy of all tests was only modest. None of this platelet function test was able to predict ischaemic stroke alone. The authors conclude that individualized antiplatelet treatment based on platelet function testing cannot be recommended to date.

Probably the most important cause of laboratory and clinical aspirin resistance is noncompliance. A recent, albeit small study, showed that drug incompliance is the predominant cause of 'pseudo-aspirin resistance' in patients undergoing coronary stenting [22]. It is well known from several prospective observational studies that persistent secondary prevention treatments including antiplatelet agents declines rapidly in the first years after stroke [23, 24].

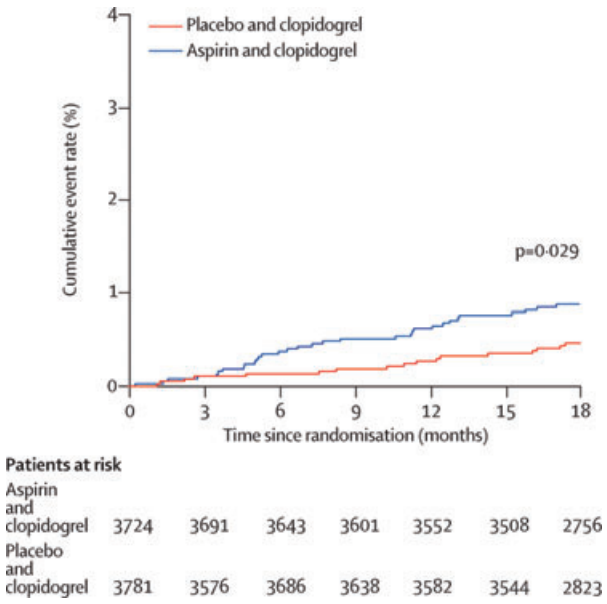

Fig. 3 Kaplan–Meier curves for cumulative rates of primary intracranial haemorrhage under clopidogrel monotherapy (Red) and the combination of aspirin and clopidogrel in the MATCH trial. Reprinted from [28]. Copyright (2004), with permission from Elsevier.

Is there a role of combining aspirin and clopidogrel in secondary stroke prevention?

Lessons learned from multiple randomized trials with antithrombotic agents in secondary stroke prevention have told us, that the more potent the antithrombotic effect of antiplatelet agents, the higher the intracranial bleeding risk (see our review about the present status of antiplatelet therapies in this issue). To date there are three antiplatelet regimens which are recommended for secondary prevention by guidelines [25, 26] and most widely used in patients with non-cardioembolic stroke: aspirin monotherapy, clopidogrel monotherapy and the combination of aspirin and dipyridamole. The combination of aspirin and clopidogrel is recommended for up to 9 months in stroke patients who were treated with stenting of the internal carotid artery or an intracranial brain artery but it is not recommended for long-term secondary stroke prevention. A systemic review about the bleeding risk of antiplatelet therapies for secondary stroke prevention which included 13 randomized trials with a follow-up of $\geq$1 year found a significantly higher total and major bleeding rate with the combination of aspirin and clopidogrel both for total bleeding and major bleeding [27]. Total bleeding rates were 4.8% with aspirin ($\leq$325 mg/day), 2.9% with clopidogrel monotherapy, 3.6% with aspirin plus dipyridamole, 10.1% with aspirin and clopidogrel and 16.8% with oral anticoagulation. Major bleeding occurred at mean rates of 1% with aspirin monotherapy, 0.85% with clopidogrel monotherapy, 0.93% with aspirin plus dipyridamole, 1.7% with aspirin plus clopidogrel and 2.5% with anticoagulation.

However, there is an ongoing debate, whether the combination of aspirin and clopidogrel should be used in the acute post-stroke and early prevention time period (*e.g.* the first 3 months after the stroke event), where the risk of stroke recurrence is highest. These considerations were partly derived from the observation that there was no early increase in life-threatening bleeding and, more specifically, in primary intracranial haemorrhage in the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH)

trial (Fig. 3) [28]. Furthermore, more than 50% of the patients in the MATCH trial were classified as having lacunar strokes due to small vessel disease, which might not be of pure atherothrombotic origin. Additionally, an increased bleeding rate has been noted in this patient group [29].

The combination of aspirin and clopidogrel has been investigated in several smaller randomized trials in the early phase after a TIA or stroke. The placebo-controlled Fast assessment of Stroke and Transient Ischemic attack to prevent Early Recurrence (FASTER) trial was designed as 2×2 factorial study to assess, whether clopidogrel (300 mg loading dose followed by 75 mg/day) and simvastatin, if started within 24 hrs of symptom onset and continued for 90 days, would reduce the risk of stroke after a TIA or minor stroke [30]. All patients also received aspirin at a dose of 81 mg/day. The trial had to be stopped prematurely due to a slow recruitment rate after 392 patients had been randomized. The primary outcome of total stroke (ischaemic and haemorrhagic) within 90 days occurred in 14 (7.1%) patients on clopidogrel and aspirin compared with 21 (10.8%) patients on aspirin monotherapy (risk ratio 0.7, 95% CI, 0.3–1.2). There were 33 ischaemic and 2 haemorrhagic strokes, both of them in patients treated with clopidogrel and aspirin.

Patients with symptomatic carotid [31] or intracranial stenosis [32] are at particular high risk of early recurrent stroke and the combination of aspirin and clopidogrel was assessed in this patient group in two smaller randomized trials [33, 34]. In both studies the detection of microembolic signals (MES) on transcranial Doppler ultrasound was used as surrogate parameter of efficacy. This surrogate parameter has just been shown to be useful in predicting subsequent ipsilateral ischaemic strokes in 467 patients with asymptomatic carotid stenosis [35].

The clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) trial randomized 107 patients with $\geq$50% carotid stenosis who had experienced an ipsilateral TIA or stroke within the last 3 months and detection of MES to receive clopidogrel (300 mg loading dose followed by 75 mg/day) or placebo in addition to 75 mg aspirin/day [33]. The primary endpoint was the proportion of patients who were MES^+ on a 1 hr recording performed 7 days after initiation of the combination therapy. In CARESS, dual antiplatelet therapy resulted in a significantly reduced proportion of MES^+ patients on day 7 (43.8% *versus* 72.7%, relative risk reduction 39.8%; 95% CI, 13.8–58.0).

A total of 100 Asian patients were randomly assigned to clopidogrel (300 mg loading dose followed by 75 mg/day) and aspirin (75–160 mg/day) or aspirin monotherapy within 7 days of symptom onset in the randomized clopidogrel plus aspirin for infarction reduction (CLAIR) trial in acute stroke or TIA patients with large artery stenosis. Two days after initiation of therapy, 14 of 45 patients in the dual antiplatelet therapy group and 27 of 50 patients in the aspirin monotherapy showed at least one MES (relative risk reduction 42.4%, 95% CI, 4.6–65.2). However, there were major limitations in the CLAIR trial. A substantial number of included patients in both treatment groups (20 of 46 patients in the dual antiplatelet and 17 of 52 patients in the monotherapy group) had no MES at baseline on central review, which was an inclusion criterion. Second, baseline variables in both groups were unevenly distributed. Thus, a larger randomized study in patients with symptomatic stenoses of brain supplying arteries is needed to finally answer the question whether the combination of aspirin and clopidogrel is superior to aspirin monotherapy in this subgroup of patients.

The randomized placebo-controlled platelet-oriented inhibition in new TIA (POINT) trial is currently assessing the efficacy of clopidogrel (600 mg loading dose followed by 75 mg/day for 90 days) and aspirin started within 12 hrs of symptom onset in patients with a TIA (NCT00991029). It is planned to include a total number of 4150 patients. The primary outcome parameter is a composite of ischaemic stroke, myocardial infarction and ischaemic vascular death.

Drug interaction between clopidogrel and proton pump inhibitors

The second-generation thienopyridine clopidogrel is a specific, irreversible antagonist of the platelet ADP $P2Y_{12}$ receptor and initiates platelet aggregation [36]. Furthermore it amplifies platelet response to other endogenous and exogenous stimuli such as TXA_2 and thrombin [37]. The prodrug clopidogrel is converted into the active metabolite by a two-step process that is mainly dependent from the hepatic cytochrome P450 (CYP) system [38]. Clopidogrel has been shown to be slightly more effective than aspirin in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial [39] and to be equally effective compared with the combination of aspirin and dipyridamole in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial [40].

Similar to aspirin resistance, clopidogrel resistance and a possible reduced efficacy of clopidogrel with concomitant use PPIs has been also a source of controversy.

Platelet inhibitors are often prescribed together with PPIs, with the goal of reducing the risk of gastrointestinal tract bleeding. However, there have been concerns that many PPIs might diminish the antiplatelet effects of clopidogrel [41, 42], possibly through inhibition of the CYP 2C19 isoenzyme and, therefore, the conversion of clopidogrel into its active metabolite [43]. A retrospective cohort study in 8205 patients discharged on clopidogrel after an acute coronary syndrome did show that concomitant use of clopidogrel and PPIs (5244 patients) was associated with a higher risk of death or rehospitalization for acute coronary syndrome (adjusted hazard ratio 1.27; 95% CI, 1.10–1.46), but not for all-cause mortality (19.9% for patients taking clopidogrel and PPI *versus* 16.6% for patients taking clopidogrel alone; adjusted odds ratio 0.91, 95% CI, 0.80–1.05) [44]. O'Donoghue and colleagues assessed the association between concomitant use of clopidogrel or prasugrel and PPIs on *in vitro* platelet aggregation in the Prasugrel in comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction (PRINCIPLE-TIMI) 44 trial and clinical outcome in a *post hoc*

analysis of the Trial to Assess Improvement in Therapeutic outcomes by optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 trial (see also below) [43]. In the PRINCIPLE-TIMI 44 trial, 201 patients undergoing elective percutaneous coronary intervention were randomly assigned to prasugrel (60 mg loading dose, 10 mg daily maintenance dose) or high-dose clopidogrel (600 mg loading dose, 150 mg daily maintenance dose). Mean inhibition of platelet aggregation measured by light-transmission aggregometry was significantly lower for patients on a PPI than for those not on a PPI at 6 hrs after a 600 mg clopidogrel loading dose (23.2 $\pm$ 19.5% *versus* 35.2 $\pm$ 20.9%, $P = 0.02$), whereas a just non-significant difference was seen in patients after the 60 mg loading dose of prasugrel (69.6 $\pm$ 13.5% with PPI *versus* 76.7 $\pm$ 12.4% without PPI, $P = 0.054$).

In the TRITON-TIMI 38 trial, a total of 13,608 patients with an acute coronary syndrome were randomly assigned to prasugrel or clopidogrel. The primary combined efficacy end-point was death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. In this study, 4529 (33%) patients were on a PPI at randomization. The authors did not find an association between PPI use and risk of the primary efficacy end-point for patients treated with clopidogrel (adjusted hazard ratio 0.94, 95% CI, 0.80–1.11) or prasugrel (adjusted hazard ratio 1.00, 95% CI, 0.84–1.20) in a *post hoc* analysis. Furthermore, no independent association existed between the use of different PPIs (omeprazole, panoprazole, esomeprazole or lansoprazole) and the risk of myocardial infarction or the composite of cardiovascular death, myocardial infarction or stroke in this trial.

A recent meta-analysis that included 10 cohort studies and 3 *post hoc* analysis of randomized controlled trials with a total of 48,674 analysed patients with coronary artery disease (42% of which were PPI users) found a significantly increased risk for major adverse cardiovascular events (death, non-fatal myocardial infarction, stroke or urgent revascularization) and mortality in PPI users [45]. Major adverse cardiovascular events occurred in 21.8% of patients with concomitant PPI use compared with 16.7% of non-users (OR 1.41, 95% CI, 1.34–1.48). The impact of PPI use was, however, only significant in patients with a high cardiovascular risk.

In summary, there is no evidence from randomized trials to date that the concomitant use of clopidogrel and PPIs results in a clinical significantly decreased antiplatelet effect. However, data from cohort studies and *post hoc* analysis of randomized trial in patients with coronary heart disease suggest a decreased efficacy if clopidogrel is used together with PPIs. There are no data available in patients who are taking clopidogrel monotherapy for secondary stroke prevention. One has to keep in mind, that the vast majority of patients with an acute coronary syndrome are treated with dual antiplatelet therapy (aspirin and clopidogrel). As a consequence, a randomized trial to address this important issue is needed. Furthermore, PPIs should not be prescribed routinely to patients treated with clopidogrel monotherapy or the combination of aspirin and clopidogrel but only after a careful risk-benefit assessment on an individual patient basis.

New antiplatelet agents for secondary stroke prevention

ADP receptor antagonists

The class of thienopyridines irreversibly inhibits the platelet ADP $P2Y_{12}$ receptor (Fig. 1). The first- and second-generation thienopyridines ticlopidine and clopidogrel have been investigated in secondary stroke prevention trials and found to be more effective compared with aspirin (see other review). Similar to clopidogrel, the third-generation oral thienopyridine prasugrel is also a prodrug that is metabolized by the CYP system to form its active metabolite (R-138727). However, prasugrel achieves greater and more consistent platelet inhibition than clopidogrel [46]. This difference might partly be caused by a distinct and more efficient conversion of prasugrel into its active metabolite by a two-step biotransformation [38]. Prasugrel has been widely studied in patients with coronary heart disease, but so far there is no distinct randomized trial available in secondary stroke prevention. The aforementioned TRITON-TIMI 38 trial compared prasugrel (60 mg loading dose and a 10 mg daily maintenance dose) to clopidogrel (300 mg loading dose and a 75 mg daily maintenance dose) in 13,608 patients with scheduled percutaneous coronary intervention [47]. Treatment with prasugrel resulted in a significant reduction of the primary combined vascular end-point (9.9% in patients treated with prasugrel *versus* 12.1% in patients receiving clopidogrel; hazard ratio 0.81; 95% CI, 0.73 -0.90). However, major bleeding was significantly more frequently observed in patients receiving clopidogrel (2.4% *versus* 1.8%; hazard ratio 1.32; 95% CI, 1.03–1.68). A *post hoc* analysis from the TRITON-TIMI 38 trial in 518 patients with a history of ischaemic stroke or TIA revealed a lack of efficacy and an increased risk of major bleeding in this subgroup of patients [48]. However, this *post hoc* subgroup analysis comprised only 3.8% of the entire study population. Based on these results, prasugrel cannot be recommended for use in secondary stroke prevention.

Beside the thienopyridines, there are two reversible non-thienopyridine ADP receptor antagonists, ticagrelor and cangrelor, which are currently under clinical investigation in patients with acute coronary syndromes [36, 38]. As we are not aware of any ongoing or planned studies to investigate their possible use in secondary stroke prevention we will not present details in this review.

Cilostazol

Cilostazol acts on different pathophysiological pathways. It is a selective antagonist of the phosphodiesterase type 3 enzyme which prevents the inactivation of the intracellular second messenger cyclic adenosine monophosphate and irreversibly inhibits platelet aggregation. In addition, cilostazol promotes arterial vasodilation, suppressed smooth muscle cell proliferation and intimal hyperplasia in animal models [49, 50]. Cilostazol also prevented the progression of symptomatic intracranial atherosclerotic stenosis of the middle

cerebral artery when added to aspirin 100 mg/day in a randomized, double-blind and placebo controlled study [51].

Cilostazol has been studied in several Asian trials in the setting of percutaneous coronary intervention and secondary stroke prevention to find an antiplatelet agent which is able to substantially reduce the risk of aspirin-related cerebral haemorrhage. Cilostazol was first investigated in a randomized placebo-controlled trial in 1095 Japanese patients with ischaemic stroke [52]. The primary end-point was the recurrence of cerebral infarction and was significantly reduced under treatment with cilostazol (3.37%/year *versus* 5.78%/year, relative risk reduction 41.7%, 95% CI, 9.2–62.5). The rate of intracranial haemorrhage was not significantly different in both treatment arms (four under cilostazol and six under placebo).

Compared with standard-dose aspirin (100 mg/day), random assignment to cilostazol (100 mg bid) showed no significant difference in the rate of stroke recurrence (including ischaemic and haemorrhagic stroke and sub-arachnoid haemorrhage) in a pilot trial with 720 enrolled Chinese patients [53]. There were 11 ischaemic and 6 haemorrhagic strokes in the cilostazol group *versus* 15 ischaemic and 5 haemorrhagic strokes in the aspirin group (hazard ration 0.62, 95% CI, 0.30–1.26) during a follow-up period of little more than 1 year. All six patients with symptomatic haemorrhage had previous cerebral microbleeds detected on magnetic resonance imaging in the area where the haematoma was located.

The results of another double-blind randomized trial with cilostazol were presented on the European Stroke Conference 2010 in Barcelona. The Cilostazol Stroke Prevention Study II enrolled 2672 Japanese stroke patients with a non-cardioembolic stroke to receive either aspirin (81 mg/day) or cilostazol (100 mg bid) for a median follow-up of 2.5 years (NCT00234065) [54]. The primary end-point ischaemic or haemorrhagic stroke was statistically significant reduced under cilostazol (2.57% in patients treated with cilostazol *versus* 3.71% in patients treated with aspirin, relative risk reduction 25.7%). This difference was primarily caused by the markedly reduced rate of haemorrhagic strokes (31 *versus* 10).

Thus, cilostazol appears to be a safer antiplatelet agent in comparison with aspirin. However, there is a need for larger phase III trials comparing cilostazol with clopidogrel and the combination of aspirin and dipyridamole and in other ethnic groups.

Sarpogrelate

The antiplatelet agent sarpogrelate is a selective inhibitor of the 5-hydroxytryptamine receptor which is involved in platelet aggregation and vasoconstriction [55, 56]. Sarpogrelate has been used in Asian patients with peripheral artery disease and was also compared to aspirin in secondary stroke prevention. The S-ACCESS trial randomly assigned 1510 Japanese patients with a recent ischaemic stroke (1 week to 6 months after onset) to receive either sarpogrelate (100 mg three times daily) or aspirin (81 mg/day) for a mean follow-up of 1.59 years [57]. The primary efficacy end-point was recurrence of cerebral infarction. Sarpogrelate was not able to show non-inferiority to aspirin in the prevention of recurrence of cerebral infarction with 72 ischaemic strokes occurring in the sarpogrelate group and 58 in the aspirin group (hazard ratio 1.25, 95% CI, 0.89–1.77). The overall bleeding rate was significantly lower in patients treated with sarpogrelate (11.9% *versus* 17.3%). To date, sarpogrelate has not been investigated in other ethnic stroke populations.

Terutroban

Terutroban (S18886) is a TXA_2 receptor antagonist binding to membrane-bound G-coupled receptors. These receptors are found on the surface of platelets but also on macrophages, monocytes, vascular endothelial cells and smooth muscle cells [58]. Unlike aspirin, terutroban inhibit both TXA_2 and eicosanoids such as isoprostanes and prostanoids which are generated non-enzymatically [36]. TXA_2 and eicosanoids may be also generated by activated monocytes and macrophages in inflammatory atherosclerotic lesions and terutroban have been shown to prevent atherosclerosis by reducing inflammation and proliferation in the vessel wall of rabbits [59]. Furthermore, the administration of terutroban resulted in a significantly improved vasodilation in peripheral arteries in a small double-blind, placebo-controlled trial with 20 randomized patients [60]. Based on these multiple modes of action, terutroban was compared with aspirin in a large secondary prevention trial. The PERFORM trial randomized 19,119 patients aged $\geq$55 years with a recent ischaemic stroke ($\leq$3 months) or TIA ($\leq$8 days) to terutroban (30 mg/day) or aspirin (100 mg/day). The primary efficacy end-point is a composite of ischaemic stroke, myocardial infarction or other vascular death [61]. However, this trial has been stopped prematurely in November 2009 because interim efficacy analyses suggested that continuation of the trial would be futile [62].

SCH 530348

Thrombin is a key factor in thrombus formation. In addition to generating fibrin, thrombin is also a very potent stimulus for platelet activation *via* binding to the PAR1 receptor on the surface of platelets [63]. SCH 530348 is a selective and competitive antagonist of the platelet PAR1 receptor but is not affecting the formation of fibrin. Thus, SCH 530348 could have the potential for a favourable balance of antithrombotic efficacy and risk of bleeding [64]. Data from the phase II trial which enrolled 1030 patients aged $\geq$45 years who were undergoing non-urgent percutaneous coronary intervention did suggest a low bleeding rate. The primary end-point (incidence of clinically significant major or minor bleeding) was seen in 2–4% of patients treated with three different doses of SCH 530348, which was not statistically different from the bleeding rate of 3% in placebo patients [65].

SCH 530348 is currently evaluated in the randomized placebo-controlled phase III Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients with Atherosclerosis (TRA 2°P-TIMI) 50 trial. This trial started in 2007 and plans to enrol about 27,000 patients with established myocardial infarction, ischaemic stroke of presumed thrombotic aetiology (time period

≥2 weeks and ≤12 months after the stroke) or peripheral artery disease. The primary end-point is a composite of cardiovascular death, myocardial infarction, stroke or coronary revascularization. Among the first 12,000 randomized trial approximately 16% had an ischaemic stroke as qualifying event [64]. Trial completion is expected in 36 to 44 months from first enrolment.

Disclosures

Dr. Ralph Weber has no conflicts of interest.

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Prof. Dr. H. C. Diener has no ownership interest and does not own stocks of any pharmaceutical company.

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